Temporary occlusion of the middle cerebral artery in intracranial aneurysm surgery: time limitation and advantage of brain protection

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The risk of focal infarction secondary to the induced reversible arrest of local arterial flow during microsurgical dissection of middle cerebral artery (MCA) aneurysms was evaluated further to define the optimal approach to temporary arterial occlusion. To compare the effectiveness of brain-protection anesthetics, a group of patients treated with the intravenous agents, propofol, etomidate, and pentobarbital, administered individually or in combination, was compared to a group treated with the inhalational agent isoflurane.

Forty-nine consecutive MCA aneurysm surgeries involving the temporary clipping of the parent vessel were retrospectively reviewed. Thirty-eight patients received intravenous brain-protection (IVBP) anesthesia. Groups of patients with and without infarctions, and receiving and not receiving IVBP, were compared based on the duration and nature of temporary arterial occlusion. Postoperative radiographic evidence of new infarction was used as the threshold for failure of occlusion tolerance. The overall infarction rate was 22.4% (11 of 49 patients), including 15.8% (six of 38 patients) in the IVBP group versus 45.5% (five of 11 patients) in the isoflurane (ISO) group. In the ISO group, the mean duration of temporary occlusion was 3.9 ± 2.2 minutes for patients without infarction versus 12.2 ± 4.3 minutes for patients with focal infarction (p < 0.01). In contrast, the mean duration was 13.6 ± 10.6 minutes for patients without infarction and 18.5 ± 9.9 minutes for patients with infarction in the IVBP group. All patients in the ISO group who underwent occlusion lasting 10 minutes or longer suffered an infarction versus five of 23 patients in the IVBP group. Patients with multiple aneurysms were found to be at increased risk of developing focal infarction, whereas those treated with intermittent temporary clip application were at a decreased risk.

It is concluded that patients in whom focal iatrogenic ischemia is induced during MCA aneurysm clip ligation have a significant advantage compared with those receiving ISO when they are given pentobarbital as the primary neuroprotective agent or when they receive propofol or etomidate titrated to achieve electroencephalographic burst suppression, particularly if more than 10 minutes of occlusion time is required. It is also concluded that 10 minutes is a general guideline for safe, temporary occlusion of the MCA. The use of intermittent temporary arterial occlusion and patients with multiple aneurysms need further evaluation before specific recommendations can be made.

Key Words * temporary arterial occlusion * cerebral ischemia * intracranial aneurysm * brain protection
The deliberate, reversible arrest of local arterial flow during microsurgical dissection of intracranial aneurysms has proven to be a valuable technique; however, safe time limits for temporary arterial occlusion have yet to be defined. Previous clinical studies have reviewed various anesthetic and surgical protocols instituted during temporary focal ischemia and have measured outcome based on postoperative neurological condition and radiographic findings.[2,3,10,11,13,18-20,23,24,28-32,34,36,40,42,44,50,51] These investigators have proclaimed the value of intravenous brain-protection (IVBP) anesthesia and intraoperative electrophysiological monitoring techniques, stressed the importance of decreased tolerance to ischemia in elderly patients and those with poor Hunt and Hess grades, and reported infarction rates related to the nature and duration of arterial occlusion.

Contemporary efforts have been focused primarily on the ability of specific anesthetic agents to reduce cellular metabolic demand while maintaining adequate cerebral perfusion. Generally, intraoperative electroencephalographic (EEG) evidence of burst suppression has been regarded as an adequate measure of reduced cerebral metabolic activity. The actual medications administered vary among institutions and include, but are not limited to, barbiturates, etomidate, mannitol, antioxidants, isoflurane (ISO), and propofol. Each has been proposed to have brain-protection capabilities based on the results of various laboratory and clinical studies.[1,4,7,9,12,16,21,22,24-27,37,39,40,43,46-48,50,53-56]

With the exception of that found for barbiturates, strong evidence does not exist for the protective ability of these other agents.[1,7,9,12,25,26,35,37,38,40,43,53-56] In particular, the purported ability of ISO to guard against neural damage is very controversial. Clinical and experimental studies have demonstrated both the presence and absence of histological protection and improved neurological outcome with the use of ISO in the setting of ischemia.[4,43,54]

The duration of arterial occlusion is another variable that must be taken into consideration in any clinical analysis. Many authors have reported favorable results obtained by performing routine reversible arterial occlusion with a temporary aneurysm clip as an adjunct to safe aneurysm dissection and following intraoperative rupture.[2,3,6,10-12,18-20,23,24-32,34,36,40,44,50,51] These investigators have reported a wide range of safe occlusion time limits based, most commonly, on clinical outcome and have generally evaluated aneurysms in several arterial distributions and generalized the results to all aneurysms. Radiographic evidence of infarction and various intraoperative and perioperative monitoring techniques have been the focus of more recent studies.[10,28,32,42]

We chose to limit our analysis to aneurysms of the middle cerebral artery (MCA) for the following reasons: 1) the frequency with which they occur; 2) the lack of any major arterial collateral circulation; 3) the presence of perforating branches that are very sensitive to ischemia; and 4) the serious and easily definable neurological sequelae associated with permanent damage in the distribution of the MCA. The goal of this study was to increase the information available to the clinician to define further the optimal approach to the commonly used practice of temporary arterial occlusion during complex aneurysm surgery. We present information on the temporal nature of the safe inducement of ischemia and effective neuroanesthetic agents that will provide the clinician with general guidelines for the practice of focal arterial occlusion in aneurysm surgery.

**CLINICAL MATERIAL AND METHODS**

**Patient Population**
A retrospective review was made of all cases in which MCA clip ligation was performed by the senior author (SLG) during a 9-year period. Cases excluded from analysis included those that involved MCA aneurysm ligation without the use of temporary clipping and those that required temporary occlusion of arteries other than the MCA for clipping of aneurysms in other distributions during the same craniotomy. The analysis revealed 49 patients, 11 of whom underwent surgery prior to the institution of standard IVBP anesthetic techniques and were analyzed as a separate group for the purpose of assessing the effectiveness of this practice on surgical results and clinical outcome.

Surgical Management

All patients in whom clip ligation was performed were treated by means of a standard protocol used for cerebral aneurysms; the exception was the kind of anesthetic agent delivered. Following induction of anesthesia, intubation, and line placement, a lumbar subarachnoid drain was placed in all patients. Those patients treated by means of contemporary IVBP techniques using propofol, etomidate, or a combination of the two, underwent continuous EEG and sensory evoked potential monitoring of contralateral median nerve stimulation; leads were placed in these patients after induction of anesthesia. The patients receiving pentobarbital as the primary IVBP agent underwent surgery before routine electrophysiological monitoring. The provision of adequate brain protection was defined as administration of pentobarbital as the primary anesthetic or as a deliberate bolus prior to occlusion. In the case of propofol and etomidate, evidence of adequate brain protection was defined as the presence of EEG burst suppression prior to and during iatrogenic focal ischemia.

In the inhalational anesthetic group, ISO, narcotics, and benzodiazepines were the agents of choice. Mannitol (1 g/kg) was administered intravenously at the time of skin incision. Normovolemic, normotensive, and normothermic conditions were maintained, and patients were artificially ventilated to maintain a PaCO₂ of 30 to 35 mm Hg. A pterional craniotomy was performed and the carotid cistern and sylvian fissure were opened microsurgically. During microdissection, EEG burst suppression was achieved in the IVBP group by using the agents outlined above and confirmed prior to placement of temporary clips.

Statistical Analysis

The individual patient variables were compared using univariate and multivariate analyses for each group. Radiographic evidence of low density in the MCA distribution and the Glasgow Outcome Scale (GOS) Scores were the designated endpoints of analysis. Tests used included chi-square for categorical variables and unpaired t-tests for continuous variables with stepwise logistic regression for multivariate testing.

RESULTS

Forty-nine operations for MCA aneurysm ligation were performed with the aid of temporary clips. In 38 of these procedures, IVBP anesthesia was used. The breakdown for primary anesthetic in the IVBP group was as follows: propofol, 50% (19 of 38 patients); pentobarbital, 24% (nine of 38 patients); etomidate, 13% (five of 38 patients); etomidate and propofol, 8% (three of 38 patients), and pentobarbital and propofol, 5% (two of 38 patients). In the ISO group 100% of patients received ISO and narcotic agents. The composition of the groups did not differ by patient age, aneurysm location (proximal or distal on the MCA) or size, preoperative Glasgow Coma Scale score, Fisher CT grade, Hunt and Hess grade, the number of days post-SAH at surgery, or rate of vasospasm or hydrocephalus (Table 1).
The total cohort consisted of 17 men (34.7%) and 32 women (65.3%) with an average age of 47.7 ± 11.9 years. The median follow-up duration was 12 months. Eighteen patients (36.7%) underwent postligation angiography, which demonstrated complete obliteration. Nineteen (38.8%) of 49 patients had multiple aneurysms. The mean aneurysm size was 10 ± 4 mm (maximum diameter) and ranged from 3 to 21 mm; 24 aneurysms (49%) were described as proximal on the MCA. Temporary clips were placed distal to the lenticulostriate arteries in 12 (24.5%) of 49 patients, whereas 37 (75.5%) of 49 were occluded at the M1 segment of the MCA. Thirty-two patients (65.3%) underwent one continuous episode of temporary occlusion, and 17 (34.7%) of 49 had intermittent clip placement with periods of reperfusion. Intraoperative rupture occurred in five patients (10.2%) (Table 2).

| TABLE 1 | CHARACTERISTICS IN TWO GROUPS OF PATIENTS UNDERGOING TEMPORARY ARTERIAL OCCLUSION* |
|-------------------------------|--------------------------------------|-------------------------------|
| Characteristic                 | IVBP (n.o. of patients) | ISO (n.o. of patients)        |
| mean age (yrs)                | 47.4 ± 12.2                | 48.9 ± 11.5                   |
| mean aneurysm size (mm)       | 10.4 ± 4.0                 | 8.8 ± 4.6                     |
| unruptured status             | 21.1% (8 of 38)            | 27.3% (9 of 11)               |
| multiple aneurysms            | 36.8% (14 of 38)           | 45.5% (5 of 11)               |
| SAH Grade†                    | 0                       | 23.7% (9 of 38)               |
| I                             | 47.4% (18 of 38)           | 54.5% (6 of 11)               |
| II                            | 5.3% (2 of 38)             | 9.1% (1 of 11)                |
| III                           | 21.1% (6 of 38)            | 9.1% (1 of 11)                |
| IV                            | 2.6% (1 of 38)             | 0                             |

* Data are presented as the mean ± standard deviation.
† Grade is based on the Hunt and Hess classification.

The overall infarction rate was 22.4% (11 of 49 patients); including 15.8% (six of 38 patients) in the IVBP group and 45.5% (five of 11 patients) in the ISO group. Six of the infarctions in the ISO group were cortical (54.5%), three were subcortical (27.3%), and two had involvement in both regions (18.2%). In the ISO group, the mean duration of temporary occlusion was 3.9 ± 2.2 minutes in patients without
infarction and 12.2 ± 4.3 minutes for patients with focal infarction (p < 0.01). In contrast, the values were 13.6 ± 10.6 and 18.5 ± 9.9 minutes, respectively, in the IVBP group.

The mean temporary clip placement time in patients in whom there was no infarction was significantly longer in the IVBP group than in the ISO group, 3.9 ± 2.2 minutes versus 13.6 ± 10.6 minutes, respectively (p < 0.05).

Five (83%) of six patients in the IVBP group who underwent iatrogenic occlusion lasting 12 minutes or longer showed radiographic and clinical evidence of infarction in the distribution in which temporary ischemia was induced. All five patients in the ISO group who underwent occlusion lasting 10 minutes or longer suffered an infarction versus five (22%) of 23 patients in the IVBP group. Eight (80%) of 10 patients in the IVBP group who underwent occlusion lasting 20 minutes or longer, tolerated the ischemia without suffering infarction.

The presence of multiple aneurysms was associated with an increased risk of focal infarction (p < 0.05). More than one aneurysm was identified on preoperative angiography in eight (72.7%) of 11 patients in the group with infarction and in 11 (28.9%) of 38 patients without infarction. Other aneurysms were clipped during the same craniotomy without the aid of temporary occlusion in four patients in the group with infarction and three patients in the group without infarction. All other patients had incidental unruptured aneurysms in the opposite hemicranium.

Statistical Analysis

Univariate analysis disclosed that advanced age, intraoperative aneurysm rupture, number of days post-SAH at time of surgery, aneurysm size, ruptured versus unruptured status, and poor Hunt and Hess grade were not independent predictors of infarction or poor outcome in this population of patients. There was a trend toward a decreased infarction rate in those patients who underwent intermittent temporary clip placement and clip placement distal to lenticulostriate branches (p < 0.07); however, because of the relatively small number of patients in whom these procedures were used, they were not statistically significant predictors in the univariate analysis (Fig. 1). The same was also true when the patients were stratified by brain protection in the univariate analysis. However, stepwise logistic regression analysis revealed that when the use of brain protection was controlled for, patients who underwent intermittent temporary clip application with periods of reperfusion had significantly less chance of developing an infarction than those who underwent one continuous episode of occlusion (p < 0.05).
All patients in whom evidence of new infarction was seen on postoperative imaging studies developed new neurological findings within 24 hours after surgery. Three patients developed hemiparesis, four experienced dysphasia to varying degrees, and five had an alteration in mental status. Fifteen patients (31%) had postoperative vasospasm. The overall outcome measured by the GOS score at the patients’ latest clinical visit (median 12 months, one patient lost to follow up) indicated that 90% had good recovery and independent status (GOS 4 or 5) and 10% had poor recovery (GOS 1, 2, or 3)(Table 3). No statistical difference existed in outcome between the IVBP and ISO groups or those patients with and without infarction.

### TABLE 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVBP (n.o. of patients)</th>
<th>ISO (no of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>infarction rate</td>
<td>15.8% (6 of 38)</td>
<td>45.5% (5 of 11)</td>
</tr>
<tr>
<td>Glasgow Outcome Scale score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.9% (3 of 38)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>9.1% (1 of 11)</td>
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<tr>
<td>3</td>
<td>2.6% (1 of 38)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>18.4% (7 of 38)</td>
<td>27.3% (3 of 11)</td>
</tr>
<tr>
<td>5</td>
<td>68.4% (26 of 38)</td>
<td>63.6% (7 of 11)</td>
</tr>
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* One patient in this group was lost to follow-up study.
DISCUSSION

Time Limitations

The incidence of infarction and the duration of ischemia in our patients are comparable to those found in previous studies, with a few distinctions. Samson, et al.,[42] studied aneurysms in several locations after induction of etomidate burst suppression. The authors demonstrated that patients routinely tolerated 14 minutes of temporary focal occlusion during clip ligation of cerebral aneurysms; this finding was almost identical to that found in our IVBP group (13.6 minutes). Also consistent with our findings, their patients in whom aneurysms were located on arteries with perforating vessel segments appeared to have poor tolerance for long occlusion times. Samson, et al., reported infarction rates of 26% and 41% in middle cerebral and basilar groups, respectively, in contrast to patients with internal carotid artery (7%) and anterior communicating complex (16%) aneurysms.

Charbel, et al.,[6] used an anesthetic protocol of mannitol and pentobarbital bolus prior to and during temporary ischemia; they determined that the maximum occlusion time without immediate postoperative neurological deficit was eight minutes in their patients undergoing temporary occlusion of the MCA. Suzuki, et al.,[51] reported that seven of 10 patients had "neurologic sequelae" after an MCA temporary occlusion time of longer than 10 minutes.

Our study supports the conclusion of these authors that the MCA is particularly vulnerable to a long occlusion time. Our IVBP group had a substantial (15.8%) incidence of focal infarction, and infarction becoming increasingly more common after only 10 minutes of iatrogenic ischemia.

Ogilvy, et al.,[32] evaluated 126 patients who underwent temporary clip ligation for aneurysms in multiple locations. These patients were treated under a protocol of hypothermia, induced hypertension, and intravenous mannitol, which had previously been shown to decrease infarction volume in rabbits.[33] Ogilvy, et al., concluded that, in general, 20 minutes was a critical threshold for focal infarction and that the risk increased for patients who experienced intraoperative rupture, were of advanced age, underwent aneurysm surgery between 4 and 10 days post-SAH, and in whom multiple clipping episodes were necessary. Three (10%) of their 29 MCA patients suffered infarction with an average occlusion time of 36.7 minutes.

These results reported by Ogilvy and coworkers represent a significant difference in infarction rate and ischemia time tolerance compared with ours and those of many previous studies. The explanation proposed for this discrepancy is the putative advantage afforded by their particular brain protection protocol. Although the explanation is plausible, especially as it relates to induced hypothermia, one must be certain that the same criteria for defining clinical infarction were used in these studies. Ogilvy, et al., excluded from analysis those patients with infarction who demonstrated new neurological deficits postoperatively that resolved within 12 hours. It is unclear whether postoperative radiographic studies were performed soon after surgery in all patients in their study. Hypodensities, possibly secondary to venous damage or retractor pressure, found on our postoperative imaging studies, were counted as infarctions as were those found by Samson, et al.;[42] however, infarction may potentially have been underestimated by Ogilvy, et al.

Cerebroprotective Agents

No previous clinical studies have compared groups of patients undergoing temporary clip ligation during aneurysm surgery in whom the intravenous agents thiopental, propofol, and etomidate have been used
with those in whom ISO was used. The relatively small number of patients in this retrospective review does not allow for comparisons of the individual medications; however, we have shown a statistically significant relationship between the use of these agents and the length of time patients can tolerate arterial flow diversion before they develop focal infarction. Our intent was not to compare the effectiveness of particular anesthetic agents; rather it was to demonstrate the efficacy of that group of medications which are routinely administered at our institution for brain protection during temporary ischemia.

The protection of brain tissue during focal ischemia has been the topic of countless investigations. Our study is consistent with several histological investigations that have failed to confirm the brain-protection capabilities of ISO.[4,43,54] Barbiturates have been studied extensively and histological evidence of their brain-protection capabilities has been documented.[16,24,26,31,43,46-48] Hypotension secondary to myocardial contractile depression and lengthy postoperative neurological recovery periods secondary to the long half-life of barbiturates have prompted the search for other agents with equal protection capability and fewer side-effects. Two agents that are widely used in our institution, propofol and etomidate, have been shown to decrease the cerebral metabolic rate of oxygen and to have the ability to produce a burst-suppression pattern on EEG monitoring; however, conclusive evidence of reduced neuronal damage following experimental ischemia has not been demonstrated.[1,7-9,12,15,21,24,27,33,37,39,40,43,53-56] Although these anesthetics are not without serious side-effects, they seem to have less effect on blood pressure than high-dose barbiturates. Propofol has been implicated in the development of angionecrotic edema,[8] and etomidate has been associated with renal failure presumed secondary to the propylene glycol vehicle, adrenal suppression, and abnormal movements by other mechanisms.[21] No patient in this population has exhibited these complications.

**Multiple Aneurysms**

The increased risk of focal infarction demonstrated in patients with multiple aneurysms cannot be easily explained. The risk does not appear to be related to the simultaneous treatment of these lesions, because the groups with and without infarction had essentially identical numbers of patients in whom multiple aneurysms were clipped during a single craniotomy. The group with infarction included a disproportionate percentage of patients who harbored unruptured, incidentally found aneurysms in the opposite hemicranium. One may theorize that patients who have the propensity to develop multiple aneurysms may have decreased tolerance to cerebral ischemia or are more sensitive to manipulation of their cerebral microvasculature, but further study would be required to substantiate such statements.

**Intermittent Reperfusion**

Analysis of parameters that significantly influenced infarction rate in our patients revealed the first clinical evidence of which we are aware that there is an advantage to allowing intermittent reperfusion during a period of reversible ischemia. In approximately one-third of the surgeries we performed we used intermittent temporary clip application, with no standardization for the number or duration of reperfusion episodes. Patients had significantly less chance of developing an infarction from undergoing intermittent temporary clip application than from undergoing one continuous episode of ischemia. Our findings contradict those of Ogilvy, et al.[32] which indicated that multiple clipping episodes were associated with a statistically significant increased risk of infarction and those reported by Sampson, et al.[42] which indicated a nonsignificant trend for the development of infarction in repetitive temporary clip
The role of intermittent reperfusion during iatrogenic ischemia is currently an area of some controversy and has been investigated in various animal models. Goldman, et al., attempted to reproduce a situation analogous to that of induced temporary ischemia in humans during aneurysm surgery and demonstrated that 5 minutes of reperfusion after every 10 minutes of ischemia produced by intraluminal occlusion of the MCA in rats resulted in significantly smaller infarction volumes compared with animals undergoing continuous ischemia. The incidence of seizures, intraparenchymal hemorrhage, death, edema formation, and blood-brain barrier breakdown were not different between the groups. Steinberg, et al., have confirmed a decrease in infarction size and have shown histological evidence of decreased cortical neuronal damage in another model of interrupted focal ischemia. Conflicting results have also been reported, citing increased histological damage, edema formation, and number of deaths in other animal models of focal ischemia with reperfusion. At present, direct application of these studies to clinical situations is not possible; however, careful scrutiny of surgical protocols and results is likely to provide surgeons with valuable information about the role of reperfusion in temporary ischemia.

**Limits of Analysis**

In addition to the well-known limits of a retrospective analysis, additional factors should be considered in any investigation of the temporary cessation of arterial flow. Questions continue to arise about the true cause of infarction seen in these studies because it is nearly impossible to separate direct perforating vessel or venous injury from focal arterial ischemia as the etiology of infarction during complex aneurysm surgery. Specifically in our study, all surgeries were performed via pterional craniotomies. Many of the hypodensities that were seen on postoperative CT scans may have been secondary to ischemia following venous injury or retractor pressure during aneurysm dissection. Although clinical findings such as recovery of function within a few days after venous injuries versus after weeks to months for arterial-based brain injury may help to separate the true etiology for these postoperative CT findings, we chose to include all cases that demonstrated new hypodensities, preferring to err on the side of including all possible infarctions attributable to temporary occlusion.

One must also consider that prolonged occlusion times are often associated with more technically challenging aneurysms and that factors other than the duration of ischemia may contribute disproportionally to morbidity in these patients.

**CONCLUSIONS**

Iatrogenic arterial flow diversion via temporary clip placement is a valuable technique in intracranial aneurysm surgery and allows proper clip placement that can reduce intraoperative rupture; however, this practice is complicated by a risk of focal infarction, particularly in sensitive areas of the brain such as that territory supplied by the MCA. We conclude that patients treated by means of focal iatrogenic ischemia during aneurysm clip ligation of the MCA have a significant advantage compared with those receiving ISO, when given pentobarbital as the primary neuroprotective agent or propofol or etomidate titrated to achieve EEG burst suppression, particularly if longer than 10 minutes of occlusion time is required. We also conclude that 10 minutes is a general guideline for safe temporary arterial occlusion in the MCA. Patients with multiple aneurysms are at increased risk of infarction and those treated via intermittent temporary clip application may be at decreased risk for developing focal infarction from iatrogenic focal ischemia in the MCA. Future directions in clinical research on focal ischemia include:
improved chemical protection of brain tissue, the role of mild hypothermia and salvage of penumbral
tissue by intermittent reperfusion during iatrogenic ischemia, and improvement in intraoperative
monitoring techniques to allow intraoperative intervention prior to irreversible brain injury.

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